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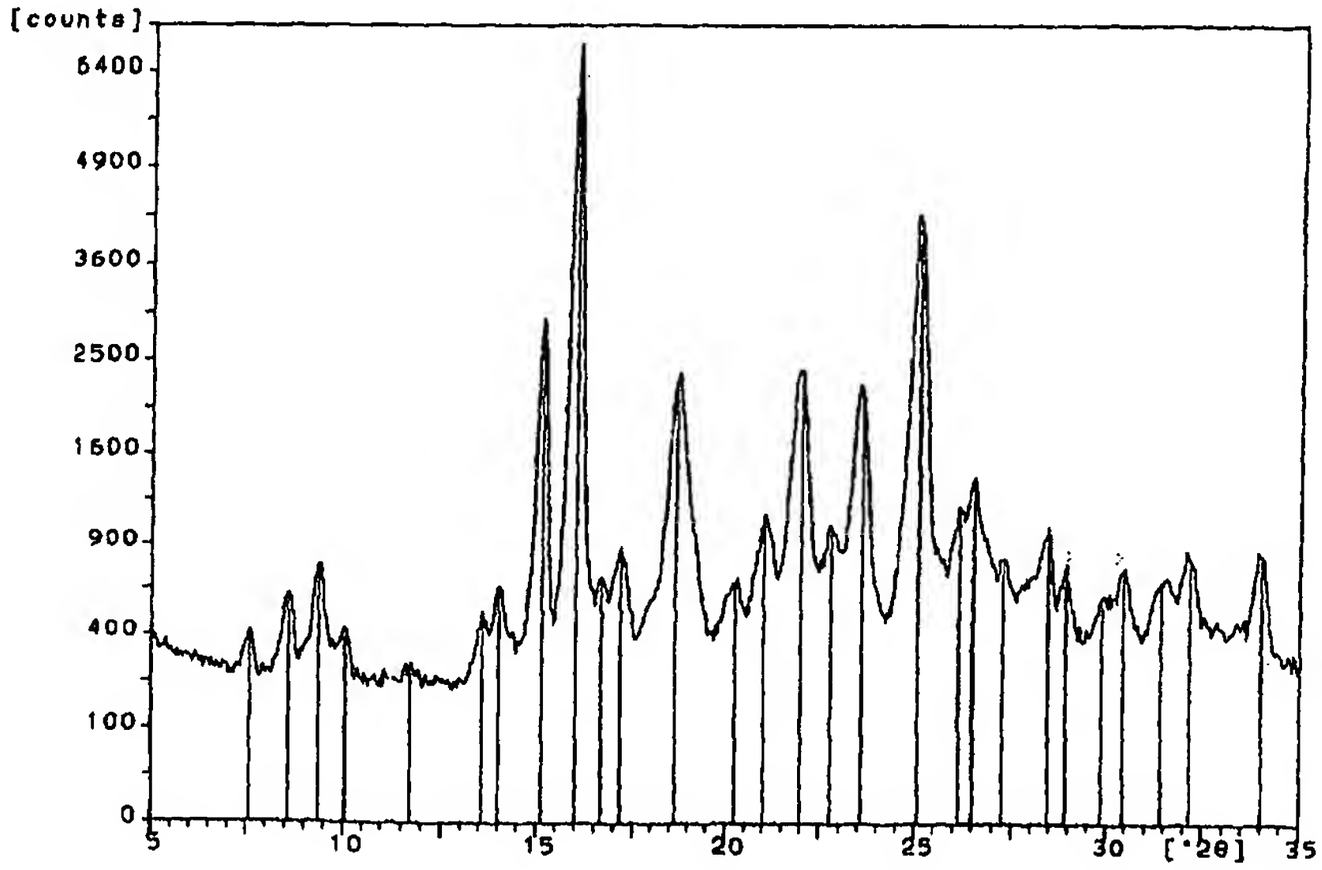
(54) Polymorphous forms of rosiglitazone maleate

(57) Three new polymorphous crystalline forms of rosiglitazone maleate, termed respectively form I, II and III and the methods for selectively obtaining each form are described and characterized. Rosiglitazone maleate may be obtained in the form of the single polymorph I by blending an approximately equimolar mixture of rosiglitazone base and maleic acid in a series of solvents and mixtures thereof which comprises isopropanol, acetone, ethyl acetate, isopropyl acetate, THF, followed by cooling of the mixture to ambient temperature; the form II may on the other hand be obtained by means of treatment of the approximately equimolar mixture of rosiglitazone base and maleic acid in water under reflux, followed by cooling of the mixture to ambient temperature; the polymorph III may be obtained by treating a mixture of rosiglitazone base with a double molar quantity of maleic acid in ethanolic solvents.

FIGURE 4



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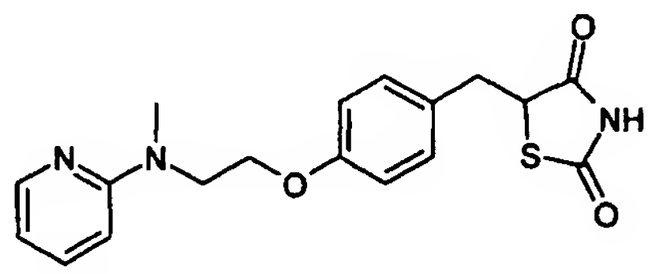
Description

FIELD OF THE INVENTION

[0001] The present invention relates to the synthesis and characterization of three polymorphous forms of rosiglitazone maleate.

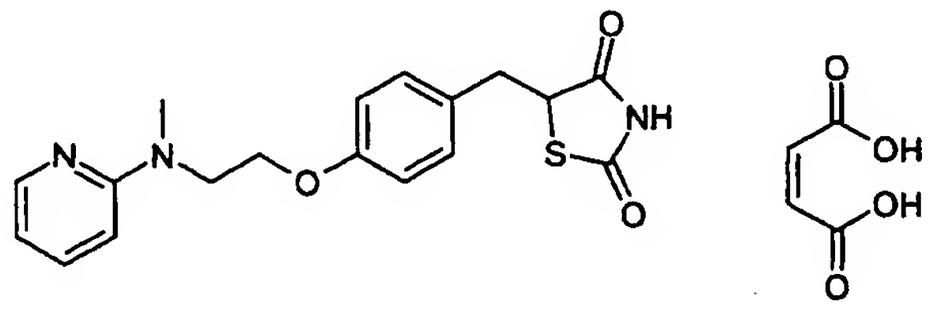
STATE OF THE ART

[0002] Rosiglitazone is a molecule of thiazolidinedione structure which forms part of the class of antidiabetics. Its structure formula is given below.



[0003] US 5,002,953 describes for the first time the compound and its use as an antihyperglycaemic. In that patent all its pharmaceutically acceptable salts are also claimed.

[0004] US 5,741,803 instead specifically describes the maleate of rosiglitazone, shown below, stating that among the possible salts, the maleate exhibits particularly favourable characteristics of stability and solubility in water.



[0005] In that patent, two examples of the preparation of the salt in question are given. In the first example the compound is prepared by hot dissolution of the rosiglitazone base mixed with maleic acid, and slow precipitation of the salt derived therefrom. After treatment of the suspension at 0-5°C for several hours, a product is isolated which, when dried under vacuum at 50°C provides a product having a melting point (m.p.) of 120-121°C. The ^{1}H-NMR of the product is provided in which a wide band between 2 and 5 ppm is found which the applicant attributes to the residual water contained in the solvent (not otherwise specified). In the second example the maleate of rosiglitazone is treated, in ethanol, with an equivalent of maleic acid, while hot, until dissolution of the solid is obtained, the mixture is decoloured with carbon and the product is precipitated by cooling to 0-5°C, then the product is filtered and desiccated, having at the end of the treatments a m.p. of 119-119.5°C.

[0006] US 6,515,132 relates to a method for the synthesis of rosiglitazone maleate, in which the step of formation of the maleate of rosiglitazone is carried out in acetone.

[0007] Polymorphic forms of rosiglitazone maleate are disclosed in WO0064892, WO0064893, WO0064896 and WO0226737 whereas WO9931093 WO9931094 and WO9931095 describe the preparation of hydrates of rosiglitazone maleate.

DESCRIPTION OF THE INVENTION

[0008] It is known in fact that many organic compounds and their salts may exist in the form of a plurality of different crystalline structures, which exhibit different physical properties and may exhibit differences also from the biological point of view.

[0009] In the course of experiments on crystallization of the maleate of rosiglitazone it was surprisingly found that this salt, under specific conditions, crystallizes in three different polymorphic crystalline pure forms, that have not been described before.

[0010] Obtaining pure crystalline forms is extremely useful, both because through these a precise characterization of the chemical-physical properties is possible, and because these characteristics may prove more favourable from a pharmacological point of view.

[0011] The subject of the present patent application are therefore three new polymorphous forms of rosiglitazone maleate, and also the methods necessary for the crystallization of these polymorphic forms.

DETAILED DESCRIPTION OF THE INVENTION

[0012] Tests on the synthesis of rosiglitazone maleate carried out starting from equimolar amounts of rosiglitazone base and maleic acid surprisingly led to the identification and characterization of two polymorphous crystalline forms of the aforesaid salt. Moreover by crystallizing mixtures of rosiglitazone base and double equimolar quantities of maleic acid a third polymorph of rosiglitazone maleate is obtained.

[0013] In particular, it was found that the maleate of rosiglitazone exists in three polymorphous crystalline modifications, which may be easily distinguished both by means of DSC, and IR, and also X-ray diffraction.

[0014] Rosiglitazone maleate exists in a polymorphous form I, which with the DSC exhibits an endothermic peak with maximum at 119°C (Figure 1), in a polymorphous form II, which with the DSC exhibits an endothermic peak with maximum at 121°C (Figure 2), and in a polymorphous form III which with the DSC exhibits an endothermic peak at 124°C (Figure 3) The DSCs were carried out with a Perkin Elmer DSC7 Differential Scanning Calorimeter.

[0015] The three forms have a powder diffraction spectrum to X-rays characterized by the principal absorptions reported in Tables 1, 2 and 3 corresponding to Figures 4, 5 and 6, respectively (Radiation Cu Kα, Generator voltage 40 kV, Divergence Slit 1°, Receiving slit 0.2 mm, scan mode step start angle 5,000, End angle 35,000, time per step 2,000 sec):

(Table 1)

FORM I		
Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.570	11.6687	2.4
8.580	10.2972	5.2
9.355	9.4458	8.1
14.005	6.3183	6.4
15.125	5.8529	41.4
16.005	5.5330	100.0
17.160	5.1631	10.0
18.625	4.7601	31.0
20.240	4.3838	6.8
21.000	4.2268	13.9
21.990	4.0387	32.9
22.785	3.8996	12.1
23.585	3.7691	30.0
25.055	3.5512	60.4
26.480	3.3632	18.0
28.425	3.1374	11.9
28.905	3.0863	8.6
30.430	2.9351	8.1
31.395	2.8470	6.7
32.145	2.7823	8.9
33.990	2.6353	9.3

(Table 2)

FORM II		
Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.615	11.5998	7.4
8.985	9.8340	4.8
9.740	9.0733	9.3
13.635	6.4889	11.6
14.015	6.3138	7.1
15.320	5.7788	100.0
17.105	5.1796	43.8
17.910	4.9485	21.8
19.255	4.6058	16.7
20.330	4.3646	27.8
20.765	4.2741	21.7
22.285	3.9859	37.8
23.730	3.7464	14.1
24.610	3.6144	37.7
25.485	3.4922	27.0
27.030	3.2960	24.4
27.440	3.2477	17.0
28.135	3.1690	8.7
29.225	3.0533	12.7
29.905	2.9854	24.1
31.645	2.8251	11.5

(Table 3)

FORM III		
Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.555	11.6918	6.2
8.895	9.9333	9.0
9.670	9.1388	12.1
13.050	6.7785	5.7
15.030	5.8896	55.2
15.345	5.7694	100.0
16.970	5.2205	40.3
17.300	5.1216	30.3
17.810	4.9761	34.7
19.105	4.6416	16.9
20.060	4.4227	33.0

(Table 3) (continued)

FORM III		
Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
20.745	4.2782	27.4
22.190	4.0028	51.0
24.400	3.6450	52.1
25.205	3.5304	36.7
25.830	3.4464	13.4
26.675	3.3391	46.0
27.360	3.2570	26.3
27.985	3.1857	13.2
29.795	2.9961	35.5
30.685	2.9112	11.4

[0016] The X-ray diffractions were carried out with a Philips PW3710 X-ray Diffractometer.

[0017] Form I exhibits with IR characteristic absorptions at the following wavelengths (Figure 7): 1744; 1618; 1262; 1178; 1083; 1070; 997, 823; 778 cm^{-1}.

[0018] Form II exhibits with IR the following characteristic absorptions (Figure 8): 1757; 1610; 1162; 1062; 1030; 926; 835; 767 cm^{-1}.

[0019] Form III, on the other hand, exhibits with IR the following characteristic absorptions (Figure 9): 1756; 1585; 1010; 921cm^{-1}.

[0020] The IR spectra were carried out with a Perkin Elmer 16 PC FT-IR spectrometer.

[0021] The solid-state ^{13}C-NMR spectra of Forms I, II and III, obtained with a Varian 400 Unity Inova, are reported in figures 10, 11, 12 and in the following tables 4, 5 and 6, respectively:

Chemical shifts (ppm):

[0022]

(Table)

FORM I				
178.5	168.1	145.4	133.0	51.5
173.9	158.9	139.1	130.7	41.1
172.5	157.6	137.1	64.5	37.2
169.7	151.3	135.1	57.6	

(Table 5)

FORM II						
177.3	166.6	151.2	133.4	114.5	63.6	51.2
175.7	158.3	147.1	131.0	113.3	57.2	42.0
172.8	157.7	138.0	117.9	109.6	55.3	40.2
169.4	153.2	136.7	115.6	66.7	52.8	37.1

(Table 6)

FORM III						
177.4	166.4	151.2	130.9	113.3	63.6	51.1
175.8	158.4	146.9	117.9	112.0	57.4	42.0
172.9	157.6	138.0	115.7	109.6	55.2	40.2
169.5	153.3	136.6	114.5	66.3	52.8	36.9

[0023] Rosiglitazone maleate may be obtained in the form of the single polymorph I by blending an approximately equimolar mixture of rosiglitazone base and maleic acid in a series of solvents and mixtures thereof, which comprises isopropanol, acetone, ethyl acetate, isopropyl acetate, THF, by heating the suspension to reflux temperature of the solvent, followed by cooling of the mixture to ambient temperature. In this way a crystalline suspension of the product is obtained which, when filtered, washed and desiccated under vacuum for 12 hours at 45-50°C provides rosiglitazone maleate form I as the single crystalline form, as confirmed by IR, XRD and DSC analyses.

[0024] Form II of rosiglitazone maleate, however, may be obtained in a pure form by treatment of the approximately equimolar mixture of rosiglitazone base and maleic acid in water under reflux, followed by cooling of the mixture to ambient temperature. The solid suspended in the mixture may be filtered, washed and desiccated under vacuum for about 10 to 14 hours, preferably 12 hours, at 45-50°C and consists exclusively of crystals of Form II of rosiglitazone maleate.

[0025] Alternatively Form II of rosiglitazone maleate may be prepared by mixing approximately equimolar quantities of rosiglitazone base and maleic acid in a water:ethanol mixture from 1.5 : 1 to 2.5 : 1 by volume, preferably 2 : 1, under reflux, followed by cooling of the mixture to ambient temperature. The solid suspended in the mixture may be filtered, washed and desiccated under vacuum for about 10 to 14 hours.

[0026] Form III of rosiglitazone maleate on the other hand may be obtained in a pure form by crystallization of rosiglitazone base and a double molar quantity of maleic acid in absolute ethanol or denatured ethanol. The mixture of the starting materials is brought to reflux, where a solution is obtained and it is then slowly cooled to room temperature; the crystalline solid thus formed is filtered, washed and dried and consists exclusively of crystals of Form III of rosiglitazone maleate.

[0027] The following experimental examples provide further clarification of the invention itself and in no way constitute any limitation thereof.

EXAMPLE 1

Synthesis of Rosiglitazone maleate Form I.

[0028] A 250 ml balloon flask equipped with mechanical stirring, coolant and thermometer, is charged with 10 g (28.0 mmoles) of rosiglitazone base, 3.25 g (28.0 mmoles) of maleic acid and 75 ml of isopropanol. The mixture is brought to reflux and maintained for 30' under such conditions. The mixture is then slowly cooled to ambient temperature and the product is filtered on a Buchner filter, washing twice with 10 ml of isopropanol. The filtered product is then desiccated for 12 hours at 45-50°C. 9.7 g of rosiglitazone maleate Form I (yield 73%) are obtained. The content of residual isopropanol in the product is 0.16% by weight.

EXAMPLE 2

Synthesis of Rosiglitazone maleate Form II.

[0029] A 500 ml balloon flask is charged with 20 g (56.0 mmoles) of rosiglitazone base and 6.50 g (56.0 mmoles) of maleic acid. To these solids are added 350 ml of water, and the mixture obtained is brought to reflux for 30'. The mixture is then slowly cooled to ambient temperature and the resultant solid is filtered on a Buchner filter, washing twice with 20 ml of water each time. A product is discharged which when desiccated under vacuum at 45-50°C for 12 hours weighs 19.9 g (yield 75%) and consists of rosiglitazone maleate Form II. The water content of the desiccated product is 0.3%.

EXAMPLE 3

Synthesis of rosiglitazone Form I.

[0030] Example 1 is repeated, using isopropyl acetate as solvent in place of the isopropanol. After desiccation, 9.5 g of rosiglitazone maleate Form I (yield 72%) are obtained.

EXAMPLE 4

Synthesis of Rosiglitazone maleate Form III.

[0031] A 500 ml balloon flask is charged with 15 g (42.0 mmoles) of rosiglitazone base and 9.70 g (84.0 mmoles) of maleic acid. To these solids are added 150 ml of ethanol, and the mixture obtained is brought to reflux for 30'. The mixture is then slowly cooled to ambient temperature and the resultant solid is filtered on a Buchner filter, washing twice with 20 ml of ethanol each time. A product is discharged which when desiccated under vacuum at 45-50°C for 12 hours weighs 14.9 g (yield 75%) and consists of rosiglitazone maleate Form III.

EXAMPLE 5

Synthesis of Rosiglitazone maleate Form II.

[0032] A 500 ml balloon flask equipped with reflux condenser and dropping funnel is charged with 20 g (56.0 mmoles) of rosiglitazone base and 330 ml of deionised water. In a becker are charged 6.50 g (56.0 mmoles) of maleic acid and 23 ml of deionised water, whereby a solution is formed. The solution obtained is then charged in the dropping funnel. The suspension of rosiglitazone base in water is heated to reflux and from the dropping funnel the solution of maleic acid is added in approximately 5'. The mixture is then slowly cooled to ambient temperature and the resultant solid is filtered on a Buchner filter, washing twice with 20 ml of water each time. A product is discharged which when desiccated under vacuum at 45-50°C for 12 hours weighs 20.5 g (yield 77%) and consists of rosiglitazone maleate Form II. The water content of the desiccated product is 0.4%.

EXAMPLE 6

Synthesis of Rosiglitazone maleate Form II.

[0033] A 500 ml balloon flask is charged with 20 g (56.0 mmoles) of rosiglitazone base and 6.50 g (56.0 mmoles) of maleic acid. To these solids are added 160 ml of water and 80 ml of absolute ethanol. The mixture obtained is brought to reflux for 30' to obtain a clear solution. The solution is filtered on a panel of celite and allowed to cool to ambient temperature. The resultant solid is filtered on a Buchner filter, washed twice with 20 ml of water each time. A product is discharged which when desiccated under vacuum at 45-50°C for 12 hours weighs 21.0 g (yield 79%) and consists of rosiglitazone maleate Form II. The water content of the desiccated product is 0.3%.

Claims

1. Rosiglitazone maleate crystalline form I having a powder diffraction spectrum to X-rays with the following principal absorptions:

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.570	11.6687	2.4
8.580	10.2972	5.2
9.355	9.4458	8.1
14.005	6.3183	6.4
15.125	5.8529	41.4
16.005	5.5330	100.0

(continued)

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
17.160	5.1631	10.0
18.625	4.7601	31.0
20.240	4.3838	6.8
21.000	4.2268	13.9
21.990	4.0387	32.9
22.785	3.8996	12.1
23.585	3.7691	30.0
25.055	3.5512	60.4
26.480	3.3632	18.0
28.425	3.1374	11.9
28.905	3.0863	8.6
30.430	2.9351	8.1
31.395	2.8470	6.7
32.145	2.7823	8.9
33.990	2.6353	9.3

2. Rosiglitazone maleate crystalline form I having a powder diffraction spectrum to X-rays as shown in Figure 4.

3. Rosiglitazone maleate crystalline form I having a DSC graph as shown in Figure 1.

4. Rosiglitazone maleate crystalline form I having an IR spectrum as shown in Figure 7.

5. Rosiglitazone maleate crystalline form II having a powder diffraction spectrum to X-rays with the following principal absorptions:

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.615	11.5998	7.4
8.985	9.8340	4.8
9.740	9.0733	9.3
13.635	6.4889	11.6
14.015	6.3138	7.1
15.320	5.7788	100.0
17.105	5.1796	43.8
17.910	4.9485	21.8
19.255	4.6058	16.7
20.330	4.3646	27.8
20.765	4.2741	21.7
22.285	3.9859	37.8
23.730	3.7464	14.1
24.610	3.6144	37.7
25.485	3.4922	27.0

(continued)

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
27.030	3.2960	24.4
27.440	3.2477	17.0
28.135	3.1690	8.7
29.225	3.0533	12.7
29.905	2.9854	24.1
31.645	2.8251	11.5

6. Rosiglitazone maleate crystalline form II having a powder diffraction spectrum to X-rays as shown in Figure 5.

7. Rosiglitazone maleate crystalline form II having a DSC graph as shown in Figure 2.

8. Rosiglitazone maleate crystalline form II having an IR spectrum as shown in Figure 8.

9. Rosiglitazone maleate crystalline form III having a powder diffraction spectrum to X-rays with the following principal absorptions:

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.555	11.6918	6.2
8.895	9.9333	9.0
9.670	9.1388	12.1
13.050	6.7785	5.7
15.030	5.8896	55.2
15.345	5.7694	100.0
16.970	5.2205	40.3
17.300	5.1216	30.3
17.810	4.9761	34.7
19.105	4.6416	16.9
20.060	4.4227	33.0
20.745	4.2782	27.4
22.190	4.0028	51.0
24.400	3.6450	52.1
25.205	3.5304	36.7
25.830	3.4464	13.4
26.675	3.3391	46.0
27.360	3.2570	26.3
27.985	3.1857	13.2
29.795	2.9961	35.5
30.685	2.9112	11.4

10. Rosiglitazone maleate crystalline form III having a powder diffraction spectrum to X-rays as shown in Figure 6.

11. Rosiglitazone maleate crystalline form III having a DSC graph as shown in Figure 3.

12. Rosiglitazone maleate crystalline form III having an IR spectrum as shown in Figure 9.

13. Pharmaceutical compositions containing rosiglitazone maleate crystalline form I according to claim 1 together with pharmaceutically acceptable excipients and/or adjuvants.

14. Pharmaceutical compositions containing rosiglitazone maleate crystalline form II according to claim 5 together with pharmaceutically acceptable excipients and/or adjuvants.

15. Pharmaceutical compositions containing rosiglitazone maleate crystalline form III according to claim 9 together with pharmaceutically acceptable excipients and/or adjuvants.

16. A process for the crystallization of rosiglitazone maleate form I **characterized in that** it comprises the following steps:

a. heating to reflux an approximately equimolar mixture of rosiglitazone base and maleic acid in a solvent selected from alcohols, esters and/or ethers;
b. cooling said mixture to ambient temperature;
c. filtration and washing of the product;
d. desiccation.

17. A process according to claim 16, **characterized in that** said alcohols and/or esters are selected from isopropanol, ethyl acetate, isopropyl acetate and/or THF.

18. A process for the crystallization of rosiglitazone maleate form II, **characterized in that** it comprises the following steps:

a. heating to reflux an approximately equimolar mixture of rosiglitazone base and maleic acid in water;
b. cooling said mixture to ambient temperature;
c. filtration and washing of the product;
d. desiccation.

19. A process for the crystallization of rosiglitazone maleate form II, **characterized in that** it comprises the following steps:

a. heating to reflux an approximately equimolar mixture of rosiglitazone base and maleic acid in a water:ethanol mixture from 1.5 : 1 to 2.5 : 1 by volume;
b. cooling said mixture to ambient temperature;
c. filtration and washing of the product;
d. desiccation.

20. A process for the crystallization of rosiglitazone maleate form III **characterized in that** it comprises the following steps:

a. heating to reflux a mixture approximately containing rosiglitazone base and a double molar quantity of maleic acid in absolute ethanol and/or denatured ethanol;
b. cooling said mixture to ambient temperature;
c. filtration and washing of the product;
d. desiccation.

21. A process according to claims 16 to 20, **characterized in that** said mixture is maintained under reflux for a time ranging between about 20 and 40 minutes.

FIGURE 1

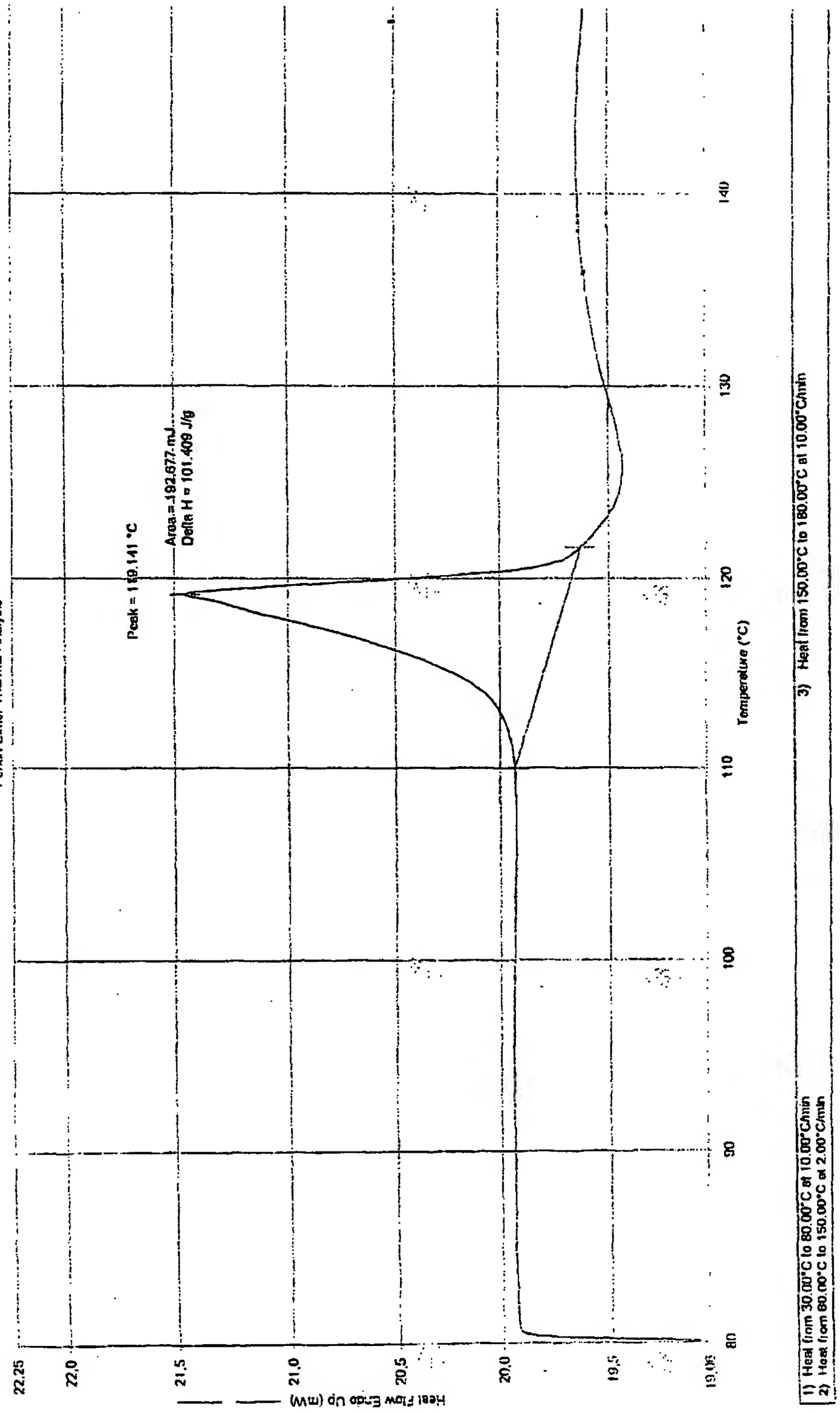

Perkin-Elmer Thermal Analysis
Peak = 119.141 °C
Area = 192.677 mJ
Delta H = 101.409 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
1) Heat from 30.00°C to 80.00°C at 10.00°C/min
2) Heat from 80.00°C to 150.00°C at 2.00°C/min
3) Heat from 150.00°C to 180.00°C at 10.00°C/min

FIGURE 2

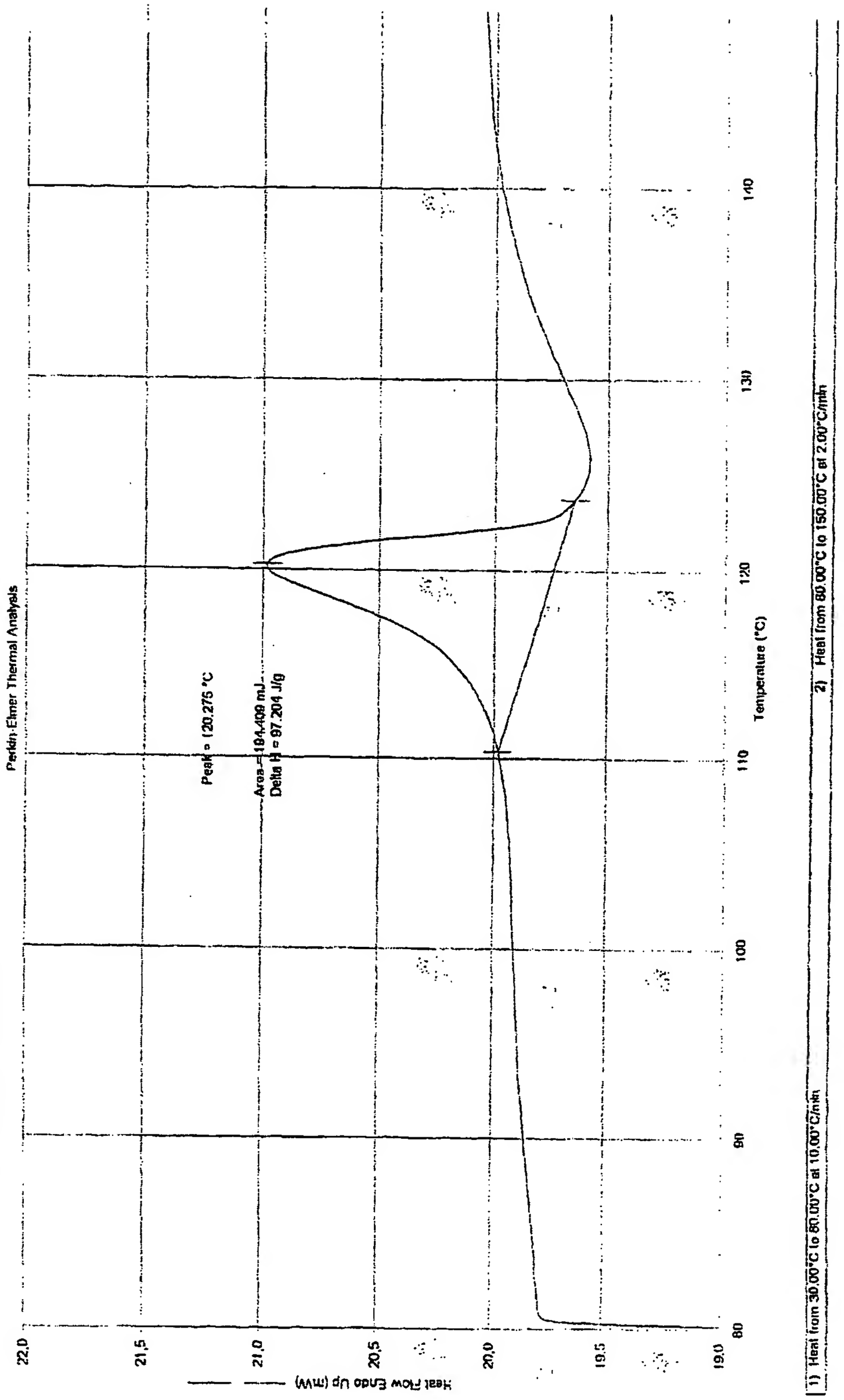

Perkin-Elmer Thermal Analysis
Peak = 120.275 °C
Area = 184.408 mJ
Delta H = 97.204 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
1) Heat from 30.00°C to 80.00°C at 10.00°C/min
2) Heat from 80.00°C to 150.00°C at 2.00°C/min

FIGURE 3

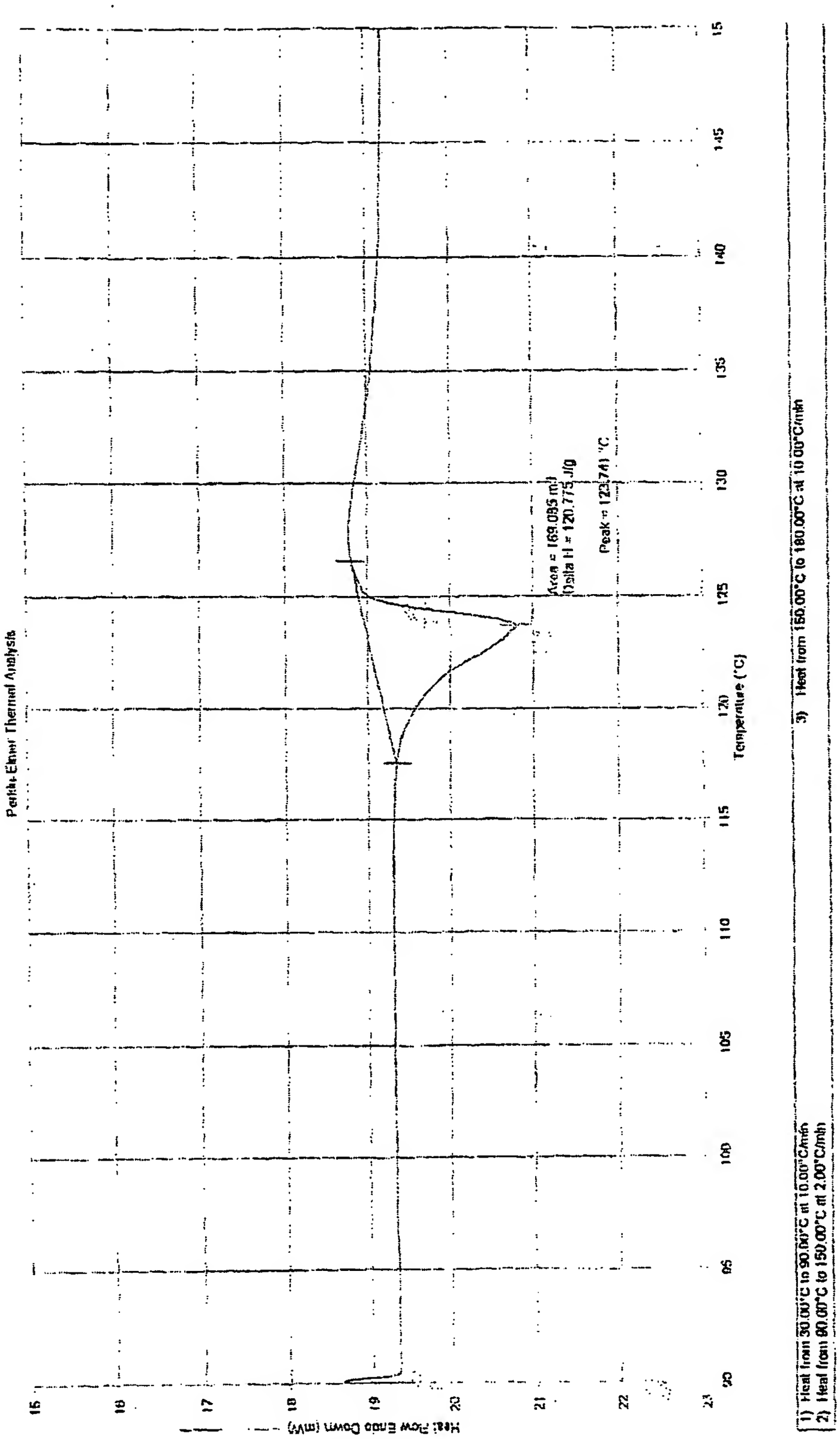
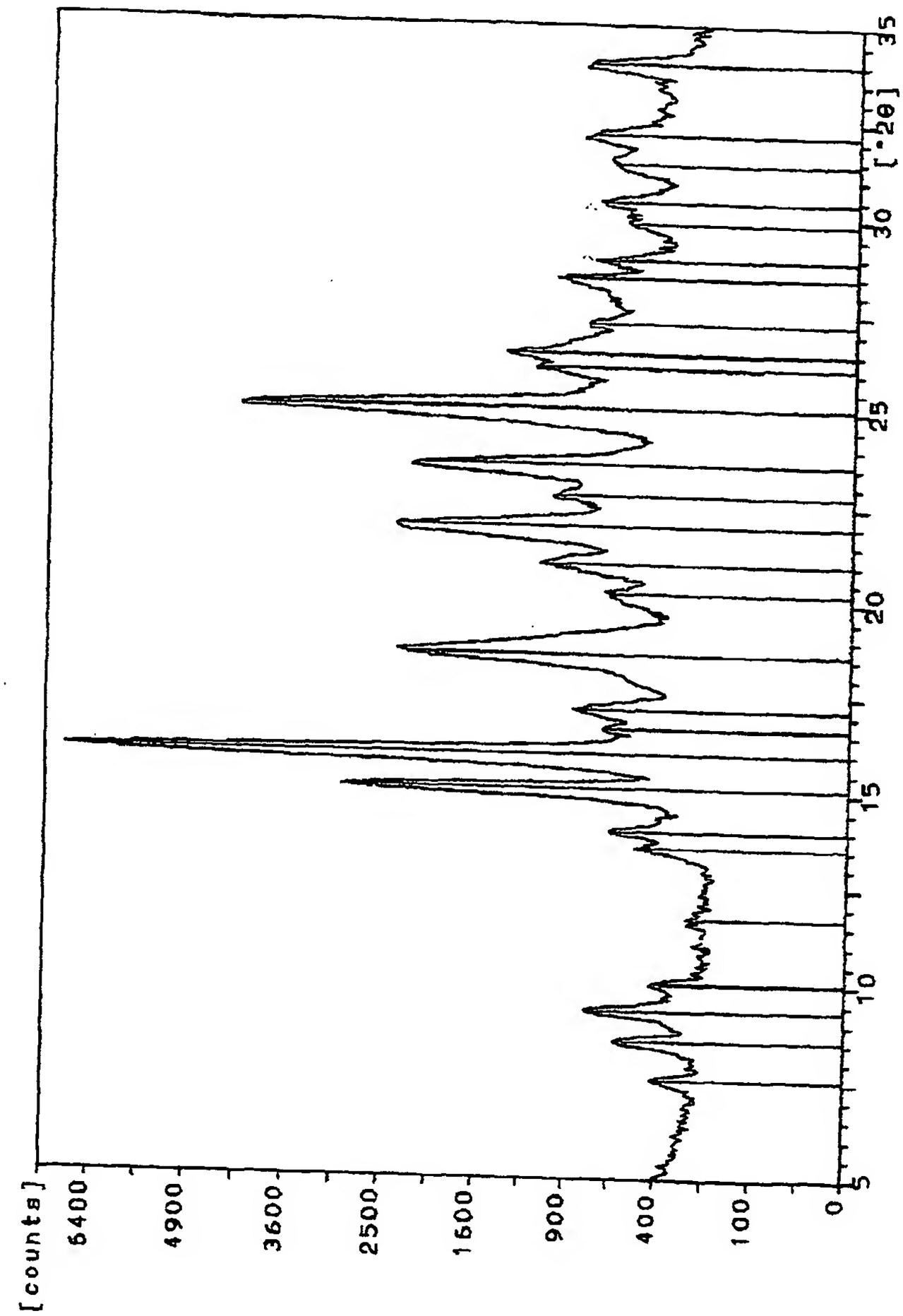

Perkin Elmer Thermal Analysis
Area = 169.095 mJ
Delta H = 120.775 J/g
Peak = 123.741 °C
Heat Flow Endo Down (mW)
Temperature (°C)
1) Heat from 30.00°C to 90.00°C at 10.00°C/min
2) Heat from 90.00°C to 150.00°C at 2.00°C/min
3) Heat from 150.00°C to 180.00°C at 10.00°C/min

FIGURE 4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30
35
[°2θ]

FIGURE 5

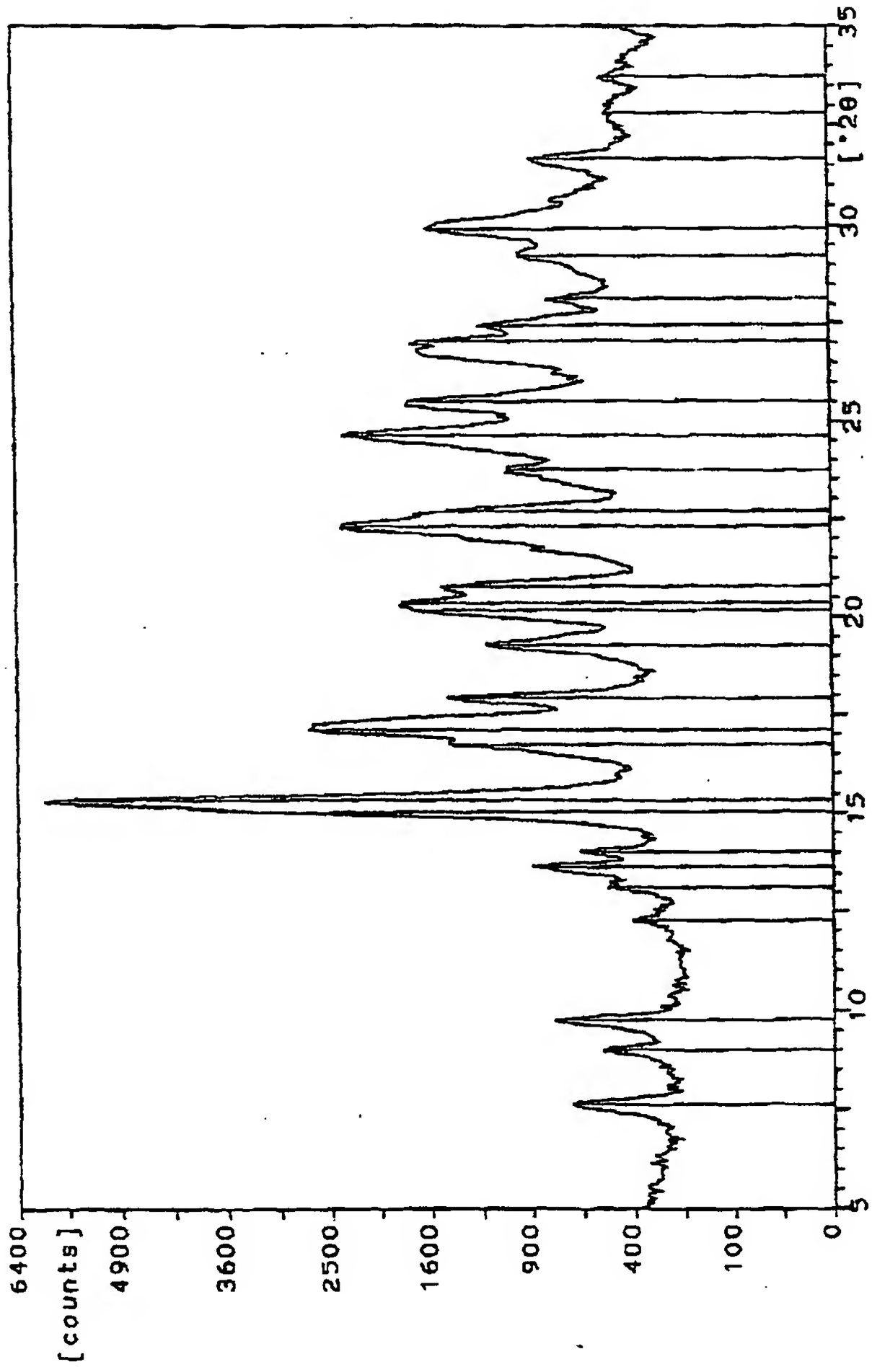

[counts]
6400
4900
3600
2500
1600
900
400
100
0
5
10
15
20
25
30
35
[°2θ]

FIGURE 6

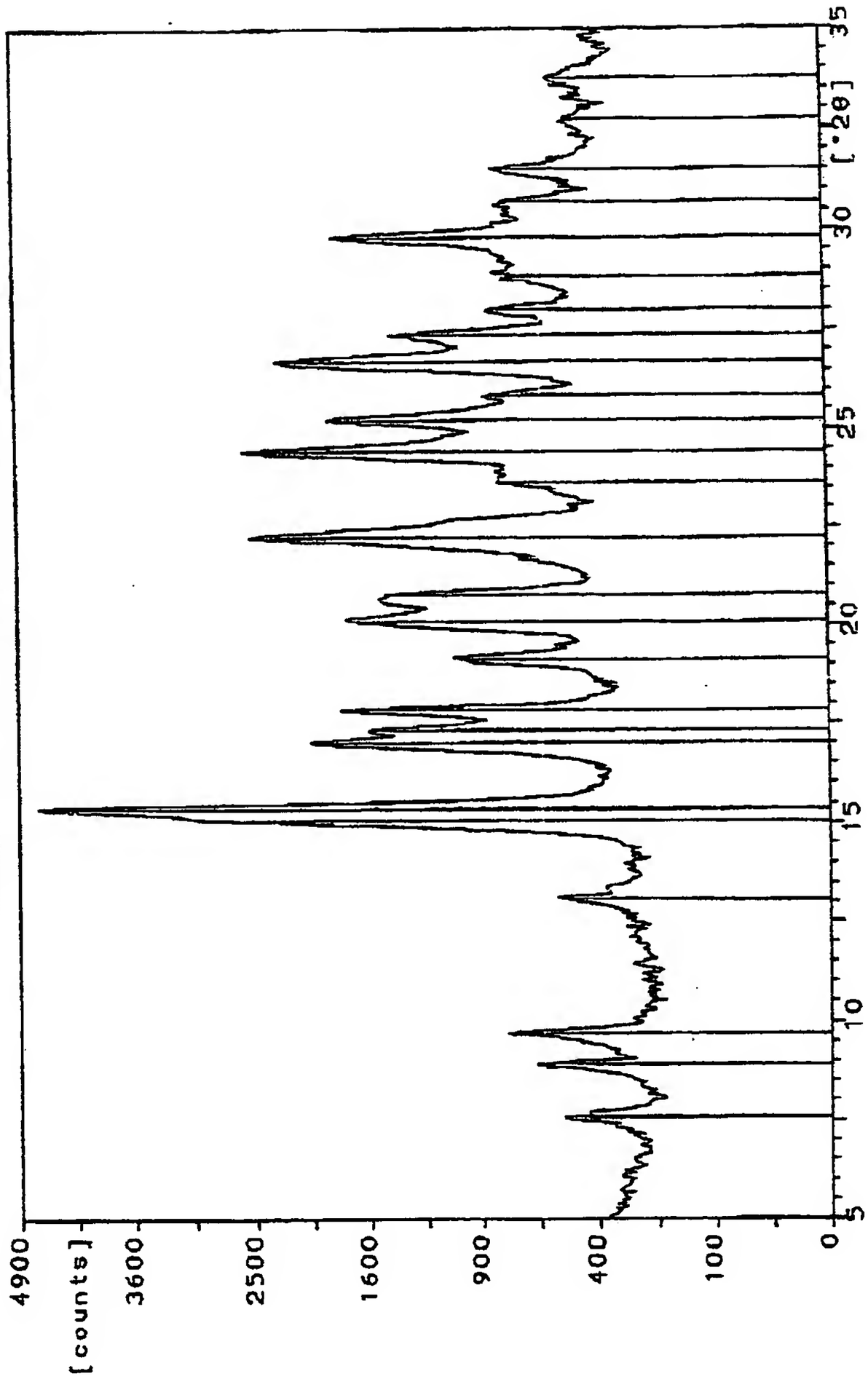
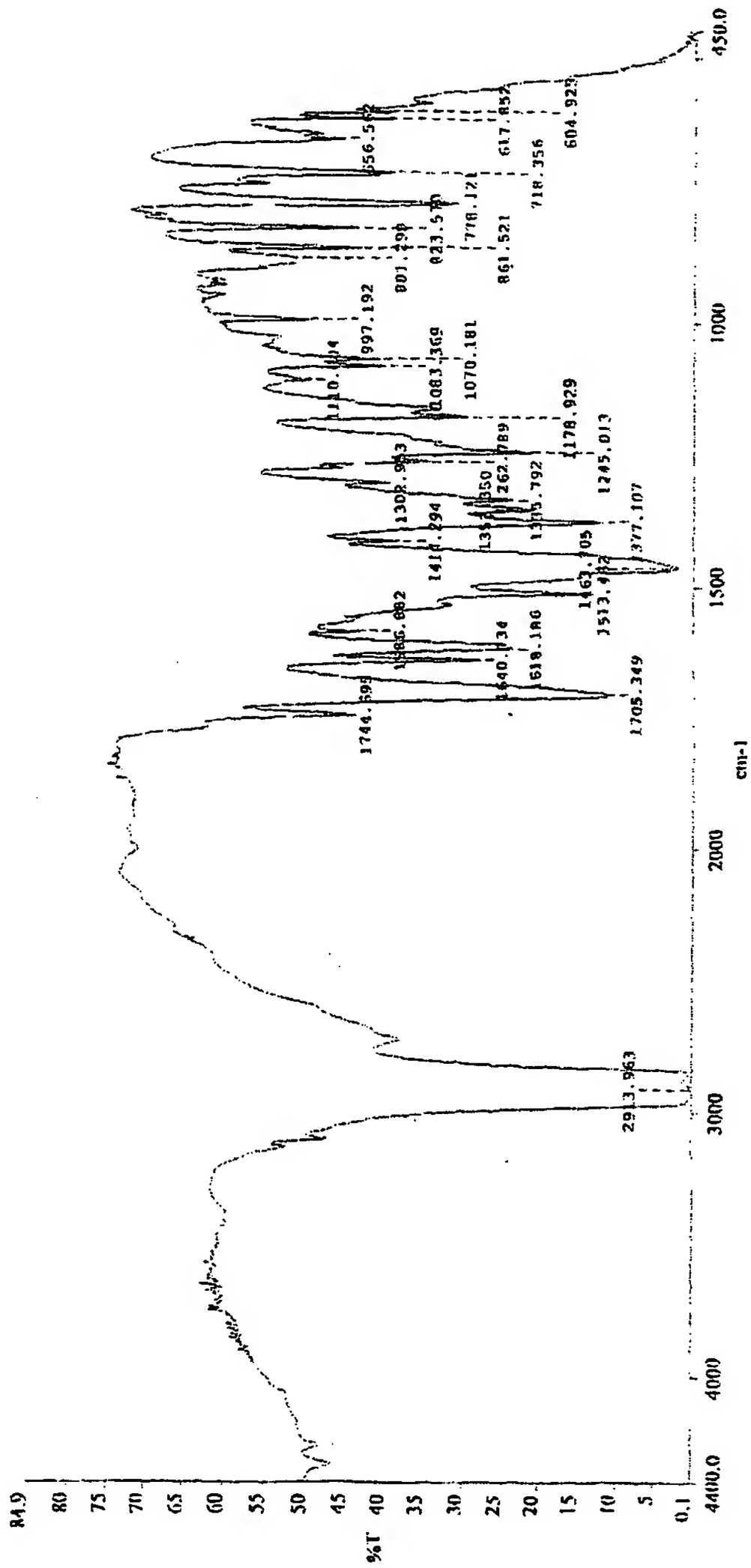


FIGURE 7

SPECTRUM IR



SPECTRUM IR

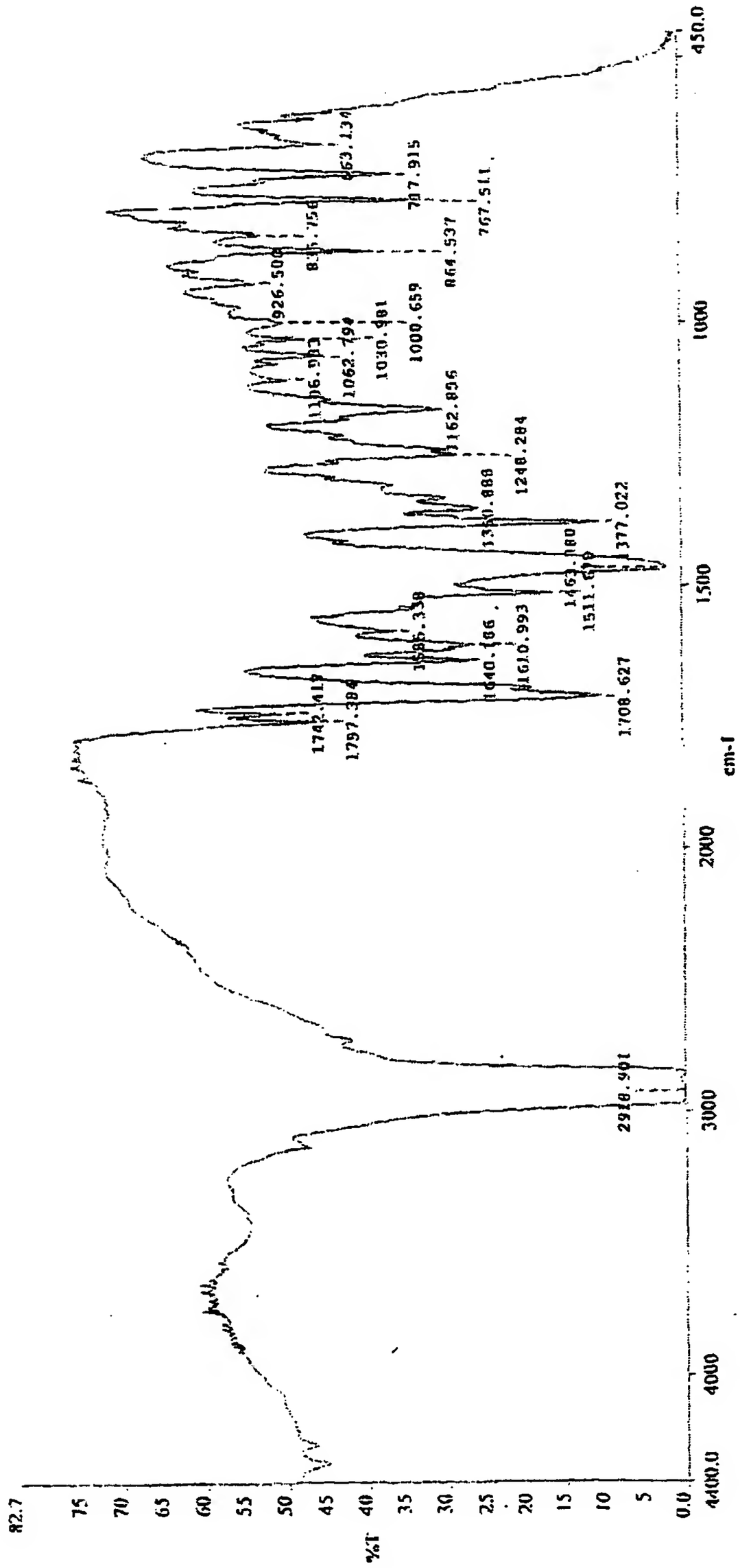


FIGURE 8

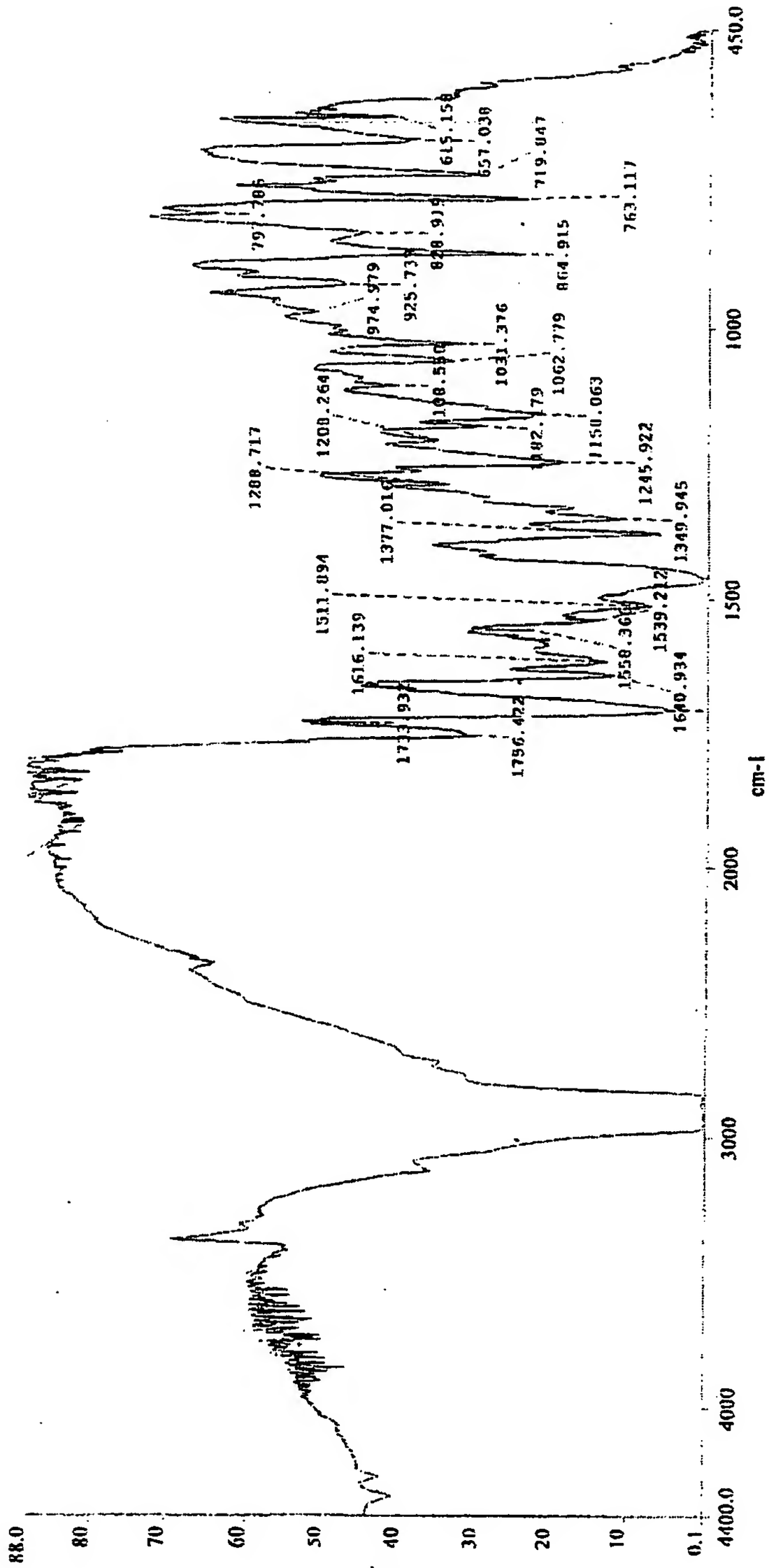

SPECTRUM IR
%T
cm-1
4400.0
4000
3000
2000
1500
1000
450.0
88.0
80
70
60
50
40
30
20
10
0.1
Spectrum Name: R142.SP
Description: ROSI 143
Resolution: 2.000 cm-1
Accumulations: 8

FIGURE 9

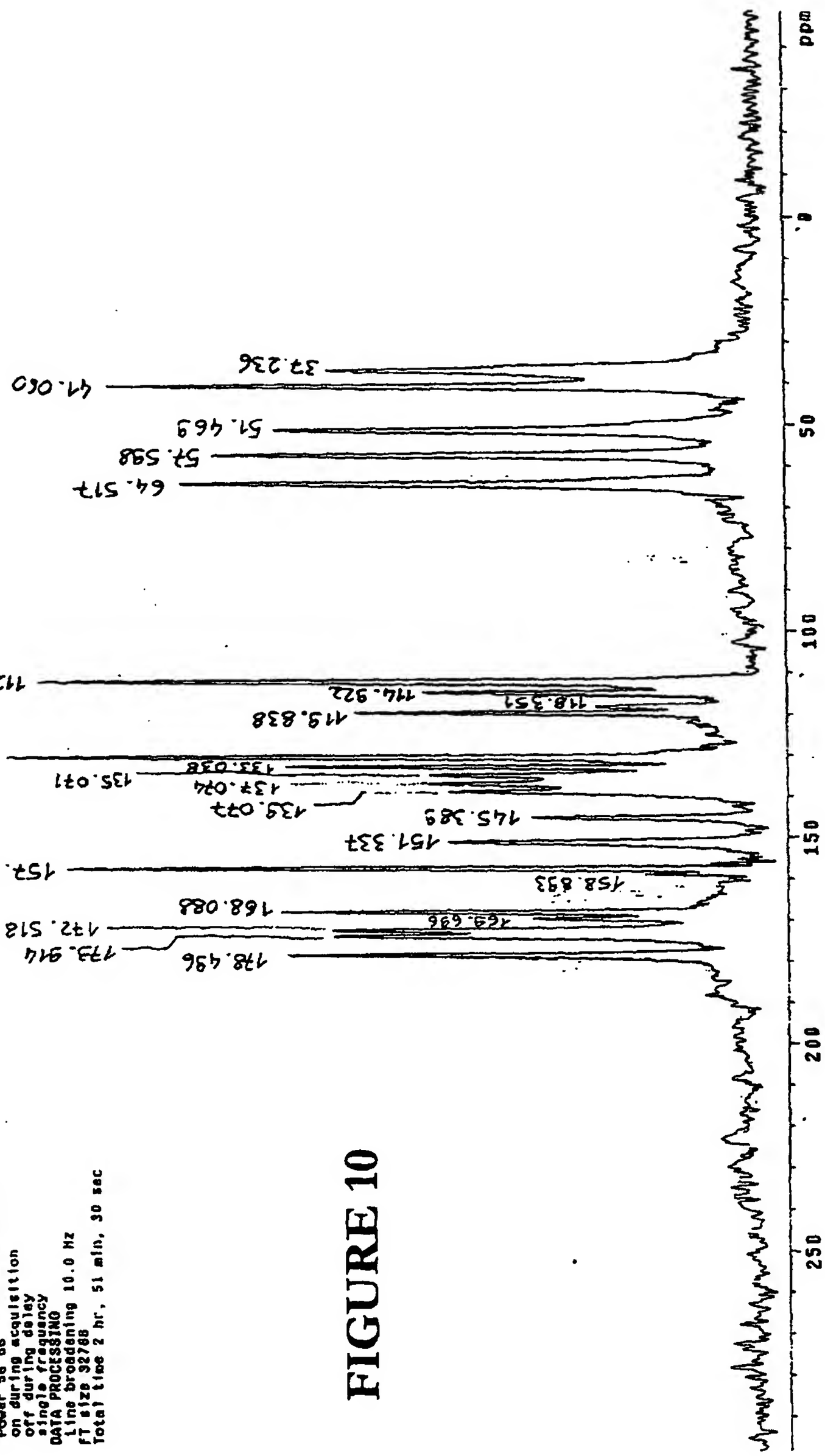
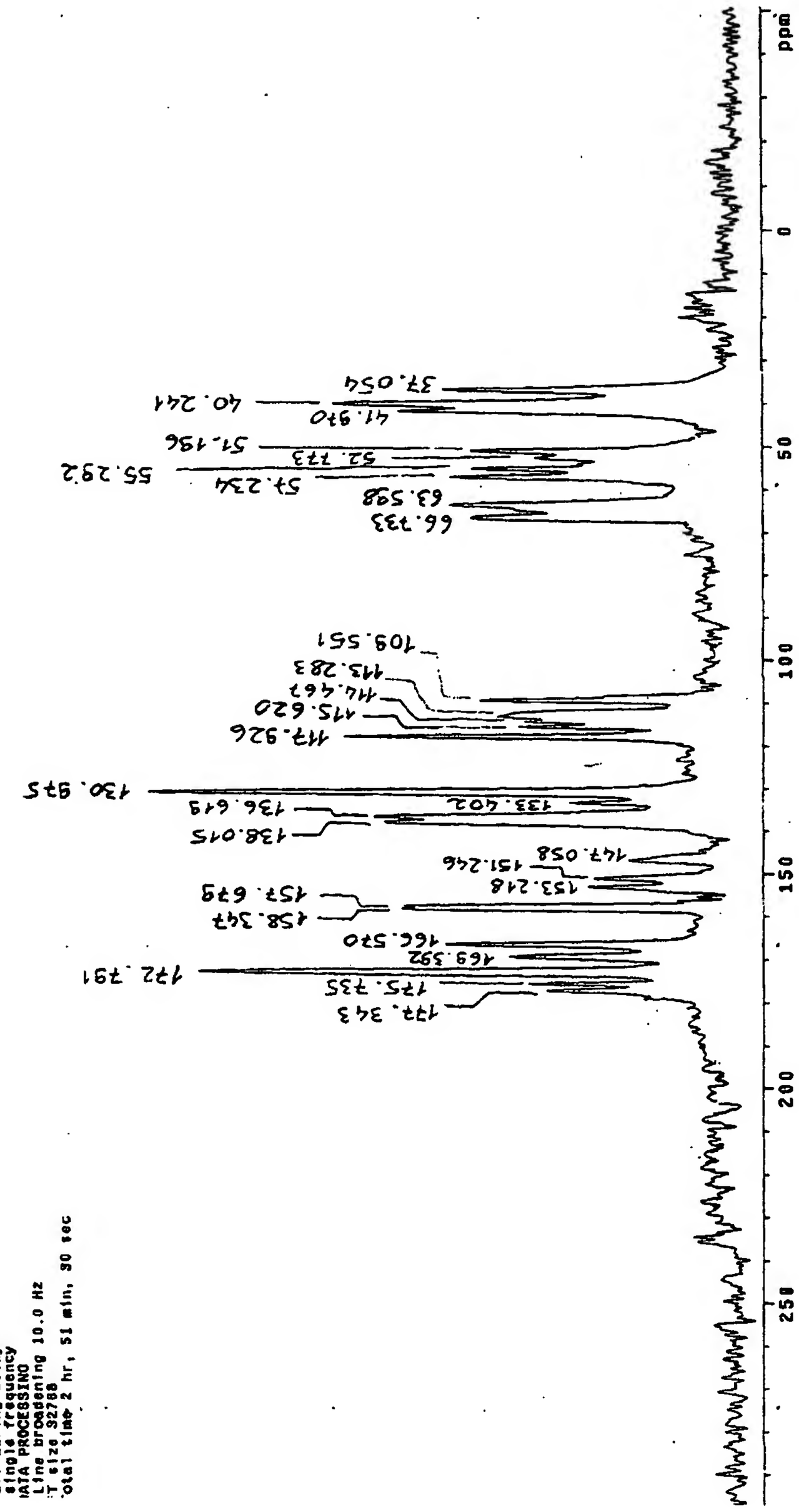
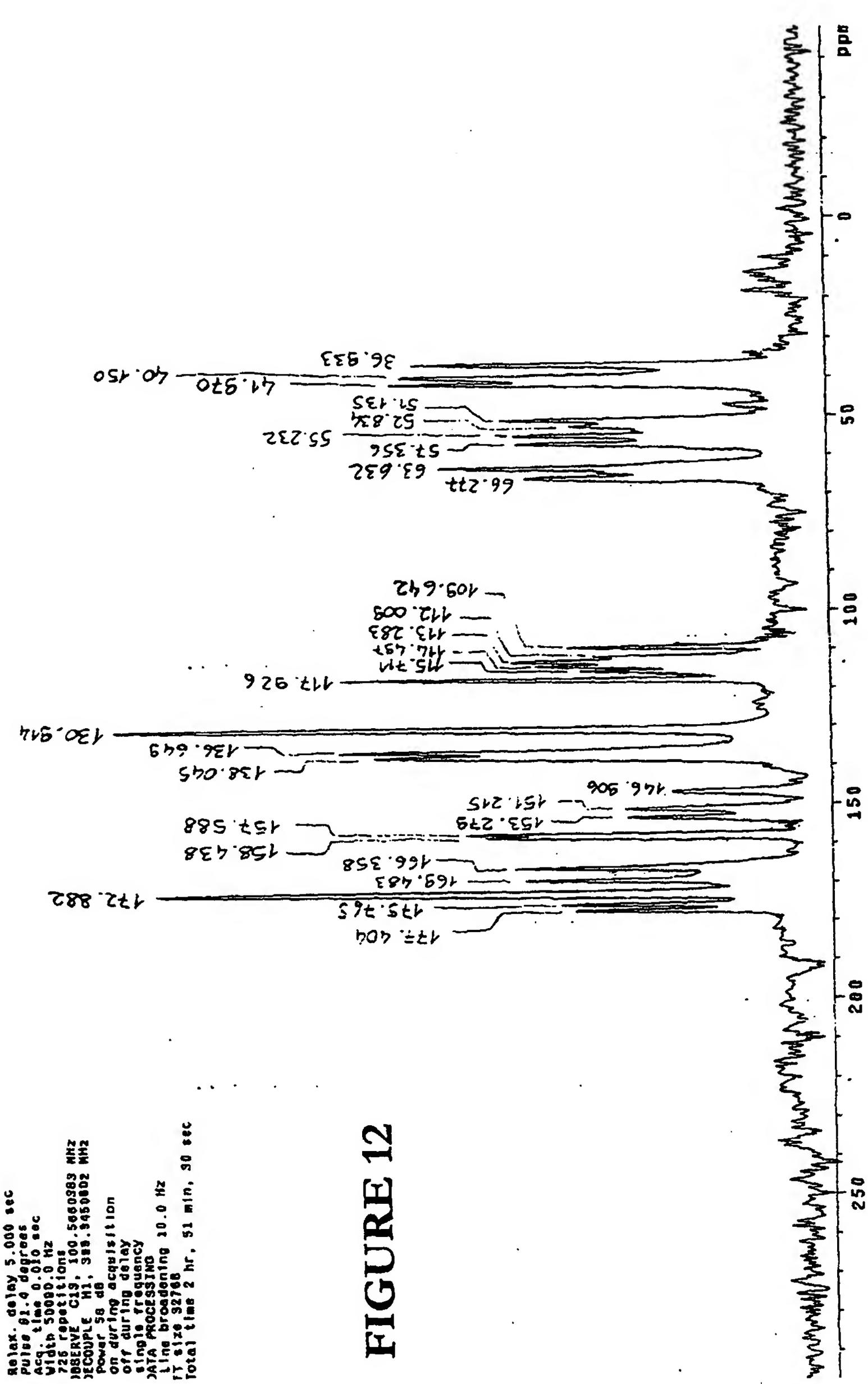

ppm
0
50
100
150
200
250
37.236
47.060
51.469
54.598
64.517
112.433
118.351
119.838
130.702
135.071
137.074
139.073
145.389
151.333
152.649
158.893
168.088
172.518
173.914
178.496
Ambient temperature
INOVA-400 "varian400"
Relax. delay 5.000 sec
Pulse 61.4 degrees
Acq. time 0.010 sec
Width 50000.0 Hz
784 repetitions
OBSERVE C13, 100.5680389 MHz
DECOUPLE H1, 399.8450802 MHz
Power 56 dB
on during acquisition
off during delay
single frequency
DATA PROCESSING
Line broadening 10.0 Hz
FT size 32768
Total time 2 hr, 51 min, 30 sec

FIGURE 10

FIGURE 11


Ambient temperature
file: camp108_114_rate4800
NOVA-400 "varian400"
Relax. delay 5.000 sec
Pulse 61.4 degrees
Acq. time 0.010 sec
Width 30000.0 Hz
865 repetitions
OBSERVE C13, 100.5860383 MHz
DECOUPLE H1, 399.8450802 MHz
Power 58 dB
on during acquisition
off during delay
single frequency
DATA PROCESSING
Line broadening 10.0 Hz
FT size 32768
Total time 2 hr, 51 min, 30 sec
ppm
0
50
100
150
200
250
172.343
175.735
172.791
169.592
166.570
158.342
152.679
153.248
151.246
147.058
138.015
133.402
136.619
130.935
117.926
115.620
114.467
113.283
109.551
66.733
63.598
54.234
55.292
52.173
51.196
41.940
40.244
37.054



Ambient temperature
INOVA-400 "varian400"

Relax. delay 5.000 sec
Pulse 81.4 degrees
Acq. time 0.010 sec
Width 50000.0 Hz
726 repetitions
OBSERVE C13, 100.5660383 MHz
DECOUPLE H1, 399.9450802 MHz
Power 58 dB
on during acquisition
off during delay
single frequency
DATA PROCESSING
Line broadening 10.0 Hz
FT size 92768
Total time 2 hr, 51 min, 30 sec

FIGURE 12

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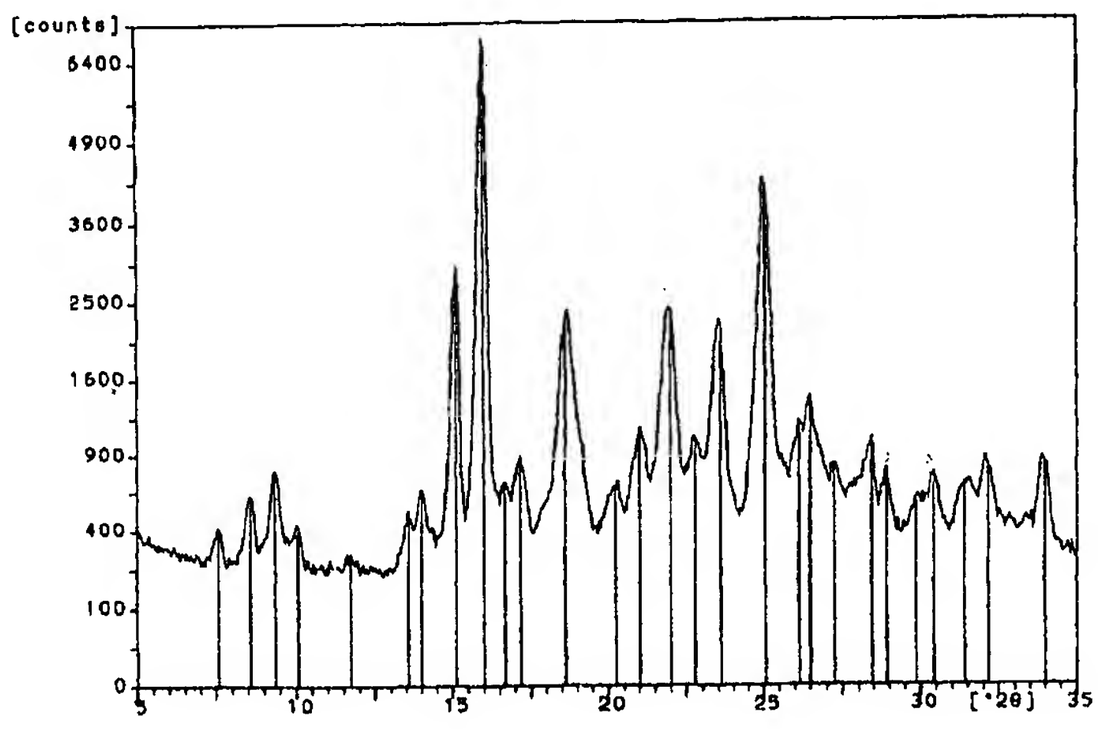
(54) Polymorphous forms of rosiglitazone maleate

(57) Three new polymorphous crystalline forms of rosiglitazone maleate, termed respectively form I, II and III and the methods for selectively obtaining each form are described and characterized. Rosiglitazone maleate may be obtained in the form of the single polymorph I by blending an approximately equimolar mixture of rosiglitazone base and maleic acid in a series of solvents and mixtures thereof which comprises isopropanol, acetone, ethyl acetate, isopropyl acetate, THF, followed by cooling of the mixture to ambient temperature; the form II may on the other hand be obtained by means of treatment of the approximately equimolar mixture of rosiglitazone base and maleic acid in water under reflux, followed by cooling of the mixture to ambient temperature; the polymorph III may be obtained by treating a mixture of rosiglitazone base with a double molar quantity of maleic acid in ethanolic solvents.

FIGURE 4



EP 1 468 997 A3

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EUROPEAN SEARCH REPORT

Application Number
EP 04 07 6138

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D,Y	WO 00/64896 A (BLACKLER PAUL DAVID JAMES ; GILES ROBERT GORDON (GB); SMITHKLINE BEECH) 2 November 2000 (2000-11-02) * claims *	1,5,9, 13-15	C07D417/12 A61K31/427 A61P43/00
D,Y	WO 02/26737 A (CHEBIYYAM PRABHAKAR ; DR REDDY S RES FOUNDATION (IN); MAMILLAPALLI RAM) 4 April 2002 (2002-04-04) * claims *	1,5,9, 13-15	
D,Y	WO 00/64892 A (BLACKLER PAUL DAVID JAMES ; GILES ROBERT GORDON (GB); SASSE MICHAEL JO) 2 November 2000 (2000-11-02) * claims *	1,5,9, 13-15	
D,Y	WO 00/64893 A (BLACKLER PAUL DAVID JAMES ; GILES ROBERT GORDON (GB); MOORE STEPHEN (G) 2 November 2000 (2000-11-02) * claims *	1,5,9, 13-15	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)
C07D
A61K
A61P

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	8 September 2004	Van Bijlen, H

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EPO FORM 1503 03.82 (P04C01)

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08-09-2004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0064896 A	02-11-2000	AT 246191 T	15-08-2003
		AU 765005 B2	04-09-2003
		AU 4130800 A	10-11-2000
		BG 106121 A	31-05-2002
		BR 0009932 A	09-04-2002
		CA 2370280 A1	02-11-2000
		CN 1356999 T	03-07-2002
		CZ 20013800 A3	17-04-2002
		DE 60004196 D1	04-09-2003
		DE 60004196 T2	15-04-2004
		DK 1173435 T3	24-11-2003
		EA 4541 B1	24-06-2004
		EP 1173435 A1	23-01-2002
		EP 1304330 A2	23-04-2003
		ES 2203453 T3	16-04-2004
		WO 0064896 A1	02-11-2000
		HK 1045153 A1	09-07-2004
		HR 20010772 A1	31-10-2002
		HU 0200931 A2	28-08-2002
		JP 2002543077 T	17-12-2002
		MA 25356 A1	31-12-2001
		NO 20015147 A	17-12-2001
		NZ 515168 A	27-02-2004
		PL 351684 A1	02-06-2003
		PT 1173435 T	31-12-2003
		SI 1173435 T1	29-02-2004
		SK 14922001 A3	05-02-2002
		TR 200103062 T2	21-05-2002
		ZA 200108719 A	21-06-2002
WO 0226737 A	04-04-2002	AU 9123201 A	08-04-2002
		BR 0114196 A	22-07-2003
		CA 2426117 A1	04-04-2002
		CZ 20030864 A3	14-01-2004
		EP 1322647 A1	02-07-2003
		HU 0301161 A2	28-11-2003
		JP 2004509961 T	02-04-2004
		NO 20031356 A	26-05-2003
		WO 0226737 A1	04-04-2002
WO 0064892 A	02-11-2000	AT 247653 T	15-09-2003
		AU 765498 B2	18-09-2003
		AU 4130600 A	10-11-2000
		BG 106119 A	31-05-2002
		BR 0009934 A	04-06-2002
		CA 2370258 A1	02-11-2000

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0064892 A		CN 1355801 T	26-06-2002
		CZ 20013799 A3	17-04-2002
		DE 60004658 D1	25-09-2003
		DE 60004658 T2	24-06-2004
		DK 1173434 T3	08-12-2003
		EA 4534 B1	24-06-2004
		EP 1173434 A2	23-01-2002
		EP 1284268 A1	19-02-2003
		ES 2204557 T3	01-05-2004
		WO 0064892 A2	02-11-2000
		HK 1045154 A1	25-06-2004
		HR 20010773 A1	31-10-2002
		HU 0200929 A2	28-08-2002
		JP 2002543075 T	17-12-2002
		NO 20015149 A	17-12-2001
		NZ 515163 A	27-02-2004
		PL 351686 A1	02-06-2003
		PT 1173434 T	31-12-2003
		SI 1173434 T1	29-02-2004
		SK 14912001 A3	05-02-2002
		TR 200103061 T2	21-05-2002
		US 2004092555 A1	13-05-2004
		ZA 200108722 A	11-09-2002
WO 0064893 A	02-11-2000	AU 4307200 A	10-11-2000
		BG 106122 A	31-05-2002
		BR 0009935 A	16-04-2002
		CA 2370262 A1	02-11-2000
		CN 1355800 T	26-06-2002
		CZ 20013801 A3	17-07-2002
		EA 3031 B1	26-12-2002
		EP 1175418 A2	30-01-2002
		EP 1277753 A1	22-01-2003
		WO 0064893 A2	02-11-2000
		HR 20010774 A1	31-10-2002
		HU 0200937 A2	28-08-2002
		JP 2002543076 T	17-12-2002
		NO 20015148 A	17-12-2001
		NZ 515167 A	27-02-2004
		PL 351685 A1	02-06-2003
		SK 14932001 A3	05-02-2002
		TR 200103060 T2	21-05-2002
		ZA 200108718 A	03-12-2002

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